Gastric Adenocarcinoma

Review and Considerations for Future Directions

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Objective: This update reviews the epidemiology and surgical management, and the controversies of gastric adenocarcinoma. We provide the relevance of outcome data to surgical decision-making and discuss the application of gene-expression analysis to clinical practice.

Summary Background Data: Gastric cancer mortality rates have remained relatively unchanged over the past 30 years, and gastric cancer continues to be one of the leading causes of cancer-related death. Well-conducted studies have stimulated changes to surgical decision-making and technique. Microarray studies linked to predictive outcome models are poised to advance our understanding of the biologic behavior of gastric cancer and improve surgical management and outcome.

Methods: We performed a review of the English gastric adenocarcinoma medical literature (1980–2003). This review included epidemiology, pathology and staging, surgical management, issues and controversies in management, prognostic variables, and the application of outcome models to gastric cancer. The results of DNA microarray analysis in various cancers and its predictive abilities in gastric cancer are considered.

Results: Prognostic studies have provided valuable data to better the understanding of gastric cancer. These studies have contributed to improved surgical technique, more accurate pathologic characterization, and the identification of clinically useful prognostic markers. The application of microarray analysis linked to predictive models will provide a molecular understanding of the biology driving gastric cancer.

Conclusions: Predictive models generate important information allowing a logical evolution in the surgical and pathologic understanding and therapy for gastric cancer. However, a greater understanding of the molecular changes associated with gastric cancer is needed to guide surgical and medical therapy.

(*Ann Surg* 2005;241: 27–39)

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ISSN: 0003-4932/05/24101-0027

DOI: 10.1097/01.sla.0000149300.28588.23

Gastric cancer is the second most common cancer worldwide, with a frequency that varies greatly across different geographic locations.[1] It is a relatively infrequent neoplasm in North America, yet contributes substantially to the burden of cancer deaths.[2–5] In North America, gastric cancer is the third most common gastrointestinal malignancy after colorectal and pancreatic cancer, and the third most lethal neoplasm overall.[4] Despite the decreasing worldwide incidence, gastric cancer accounts for 3% to 10% of all cancer-related deaths.[6] Although the survival rate for gastric cancer has steadily improved in countries such as Japan, it has not in North America.[3] The substantial mortality associated with gastric cancer has prevailed despite technical advances in surgery and the use of adjuvant therapy.

Ninety percent of all tumors of the stomach are malignant, and gastric adenocarcinoma comprises 95% of the total number of malignancies.[7] Curative therapy involves surgical resection, most commonly a total or subtotal gastrectomy, with an accompanying lymphadenectomy. The overall 5-year survival rate of patients with resectable gastric cancer ranges from 10% to 30%.[8–10]

EPIDEMIOLOGY

Gastric cancer is rare before the age of 40, but its incidence steadily climbs thereafter and peaks in the seventh decade of life.[11] It is estimated that 876,340 cases of primary gastric cancer were diagnosed in 2000, accounting for nearly 650,000 deaths worldwide.[4] In North America, the lifetime probabilities of developing and dying from gastric cancer are 1.5% and 1.0%, respectively.[4] Overall, age-standardized mortality rates have decreased in females (9.9 to 4.2 per 100,000) and males (21.2 to 9.1 per 100,000) over the past 30 years in Canada.[5] In the United States, there are 24,000 new cases and 14,000 deaths annually.[12] In a retrospective study involving more than 50,000 patients treated for primary gastric cancer, Hundahl et al[13] demonstrated that 65% of gastric cancers in the United States present at an advanced stage (T3/T4), with nearly 85% of tumors accompanied by

lymph node metastasis at diagnosis. This problem is complicated further by a recurrence rate of 40% to 65% in patients resected with curative intent.[14] In the absence of formal screening programs, most patients present with advanced pathologic stage and can expect a median survival of 24 months (20–30% 5-year survival) in tumors resected with curative intent, a median survival of 8.1 month after palliative procedures, and a median survival of only 5.4 months for advanced disease without an operation.[15–17]

RISK FACTORS

Comparative studies between Asian and Western countries demonstrate striking differences in the incidence and overall survival of gastric cancer, which suggest ethnic origin as a possible risk factor.[3,11,18] Incidence is highest in Japan (>40 per 100,000), Eastern Asia, South America, and Eastern Europe; whereas Canada (10 per 100,000), Northern Europe, Africa, and the United States have the lowest incidences.[19] The National Cancer Institute, in an examination of ethnicity as a risk factor for gastric cancer, identified 3 groups: those with high (Koreans, Vietnamese, Japanese, Native American, and Hawaiian), intermediate (Latino, Chinese, and black), and low age-adjusted incidence of gastric cancer (Filipino and white).[4]

First-generation migrants from high-incidence to low-incidence countries sustain the risk rate of their native country, whereas subsequent generations acquire the risk rate of their new environment.[11,20] This suggests the etiologic influence may reside more in environmental than ethnicity factors.[11] Several dietary and behavioral factors have since been examined in detail. In a case–control study, Ramon et al[21] identified diets rich in salt, smoked or poorly preserved foods, nitrates, nitrites, and secondary amines to be associated with an increased risk of gastric cancer. The association is believed to arise from the prolonged excessive consumption of salty or pickled foods, which leads to atrophic gastritis and an alteration in the gastric environment with the generation of carcinogenic N-nitroso compounds.[11] In contrast, diets rich in fruits and vegetables may be associated with a reduced risk of cancer. Haung et al,[20] in a retrospective survey of 877 Japanese patients with gastric cancer, suggested that frequent intake of raw vegetables and fruit significantly decreased the risk of gastric cancer-related death (hazard ratio, 0.74; 95% confidence interval [CI], 0.56–0.98) through their antioxidant effects. Calcium, vitamin A, and vitamin C have been postulated to exert a protective effect on the gastric mucosa through the reduced formation of N-nitroso carcinogenic compounds.[11,20] Case–control studies indicate that cigarette smokers have a 2 to 3 times increased risk of proximal gastric cancer.[22] These results were supported in a study by Haung et al,[20] who demonstrated an odds ratio of 2.53 (CI, 1.22–5.29) for habitual smokers and a trend toward significance in patients with habitual alcohol consumption.

Most gastric cancers occur sporadically, whereas 8% to 10% has an inherited familial component.[23] Gastric carcinoma occasionally develops in families with germline mutations in p53 (Li-Fraumeni syndrome) and BRCA2.[19] In 1% to 3% of gastric cancers, germline mutations in the gene encoding the cell adhesion protein E-cadherin leads to an autosomal-dominant predisposition to gastric carcinoma, referred to as hereditary diffuse gastric cancer, that has a penetrance of approximately 70%.[19,24–27] Huntsman et al[24] suggested that identification of the E-cadherin mutation should prompt prophylactic gastrectomy in affected kindreds. Gastric cancer can develop as part of the hereditary nonpolyposis colon cancer (HNPCC) syndrome, as well as part of the gastrointestinal polyposis syndromes, including familial adenomatous polyposis (FAP) and Peutz-Jeghers syndrome.[19]

An important development in the epidemiology of gastric carcinoma has been the recognition of the association with *Helicobacter pylori* infection.[19] Three independent studies reported a significantly increased risk in subjects who were demonstrated to have had *H. pylori* infection 10 or more years before the cancer diagnosis.[28–30] A follow-up meta-analysis of 42 observational studies carried out by Eslick et al[31] showed a significant relationship between *H. pylori* and gastric cancer (odds ratio [OR], 2.04; CI, 1.69–2.45). *H. pylori* has subsequently been shown to induce changes in the gastric mucosa and the gastric flora predisposing to the development of carcinoma in humans.[19] Furthermore, *H. pylori* is capable of adhering to the Lewis blood group antigen, and may be an important factor facilitating chronic infection and the subsequent increased cancer risk observed in patients with blood group A phenotype.[19]

Other factors associated with an increased risk of gastric cancer include chronic atrophic gastritis (eg, pernicious anemia, toxic and dietary agents, previous gastric surgery with bile reflux), hypertrophic gastropathy (Metenier's disease), gastric polyps, low socioeconomic status, and obesity.[11,19]

GASTRIC ADENOCARCINOMA: CLINICAL CONSIDERATIONS

Case Definition/Description

The diagnosis of gastric cancer requires histopathologic assessment of tissue or cytologic assessment of gastric brushing/washes. Several classification systems have been proposed to aid the description of gastric cancer either through macroscopic features (Borrmann) or on the basis of microscopic configuration (Ming, Carniero, and Goseki).[19,32] The 2 most commonly used are the Lauren and World Health Organization (WHO) systems.[19]

The Lauren classification divides gastric cancer into 2 major histologic types: intestinal or diffuse.[11,33,34] This system describes tumors on the basis of microscopic configuration and growth pattern.[11] Diffuse-type cancers have nonco-

hesive tumor cells diffusely infiltrating the stroma of the stomach and often exhibit deep infiltration of the stomach wall with little or no gland formation.[19,32] Diffuse tumors may exhibit pronounced desmoplasia and associated inflammation with relative sparing of the overlying mucosa.[32] In comparison to intestinal-type gastric cancers, diffuse-type gastric cancers are less related to environmental influences, have increased in relative incidence, occur more often in young patients, and are associated with a worse prognosis.[19] These cancers are not associated with intestinal metaplasia, are not localized to the antrum, and may arise out of single-cell mutations within normal gastric glands, as is the case for the newly described hereditary diffuse gastric carcinoma.[23,24,35]

Intestinal-type cancers show recognizable gland formation similar in microscopic appearance to colonic mucosa.[11,19,32] Glandular formation ranges from well to poorly differentiated tumors, which grow in expanding, rather than infiltrative, patterns.[6,11] Intestinal-type cancers are believed to arise secondary to chronic atrophic gastritis.[11,19]

H. pylori and autoimmune gastritis are the most common etiologic lesions that create an environment conducive to gastric inflammation. If gastritis persists, gastric atrophy occurs followed by intestinal metaplasia, which in turn may lead to dysplasia. Dysplasia can arise in either the native gastric or "intestinalized" gastric epithelium.[19] The term adenoma is applied when dysplastic proliferation produces a macroscopic protruding lesion and is described as tubular, tubulovillous, or villous adenoma morphologically.[19] Adenomas tend to occur in the distal stomach, often have a prolonged precancerous phase and an expanding growth pattern.[6,11,19] Carcinoma is diagnosed when the tumor invades into the lamina propria or through the muscularis mucosae.[19] Up to 80% of dysplastic lesions may progress to invasion.

The Lauren classification has proven useful in evaluating the natural history of gastric carcinoma, especially with regard to incidence trends, clinicopathologic correlations, and etiologic precursors.[6,11,33] Despite the apparent use of the Lauren classification, the WHO[19] has revised the definition of gastric cancer to "malignant epithelial tumors of the gastric mucosa with glandular differentiation." The WHO system assigns grades to adenocarcinoma based on the degree of resemblance to metaplastic intestinal tissue.[6,19,32] It categorizes the histologic patterns into 5 subtypes: adenocarcinoma (intestinal and diffuse), papillary, tubular, mucinous, and signet-ring cell.[19,32]

Clinical Manifestations

Gastric carcinoma often produces no specific symptoms when it is superficial and potentially surgically curable, although up to 50% of patients may have nonspecific gastrointestinal complaints such as dyspepsia.[11] In Western countries, even with endoscopic evaluation, gastric cancer is found in only 1% to 2% of patients with dyspepsia. The lack of early pathognomic symptoms often delays the diagnosis. Consequently, 80% to 90% of patients with gastric cancer present with locally advanced or metastatic tumors that have poor rates of resectability.[19] Patients may present with anorexia and weight loss (95%) as well as abdominal pain that is vague and insidious in nature. Nausea, vomiting, and early satiety may occur with bulky tumors that obstruct the gastrointestinal lumen or infiltrative lesions that impair stomach distension.[11] Ulcerated tumors may cause bleeding that manifest as hematemesis, melena, or massive upper gastrointestinal hemorrhage.

Physical examination of early gastric cancer is usually uninformative. Patients with advanced tumors may present with a palpable abdominal mass, cachexia, bowel obstruction, ascites, hepatomegaly, and lower extremity edema.[11,36,37] Peritoneal seeding may cause involvement of the ovaries (Krukenberg tumor) or pelvic cul-de-sac (Blumer's shelf) detectable on rectal examination.[37] Metastasis may manifest as an enlarged supraclavicular lymph node (Virchow's node), left axillary lymph node (Irish's node), or a periumbilical lymph node (Sister Mary-Joseph's node).[11,37]

Screening for Gastric Cancer

The goal of mass screening (asymptomatic populations) or surveillance (subjects at risk) is the detection and diagnosis of gastric cancer at an early and therefore potentially curable stage.[19] Mass screening for early detection of gastric cancer is cost-effective and recommended in high-incidence regions such as Japan and China, where as many as 50% to 80% of detected malignancies are early gastric cancers.[19] In North America, there are no formal screening programs. The American Society for Gastrointestinal Endoscopy recommends endoscopic surveillance for high-risk individuals (history of gastric adenoma, FAP, HNCC, Peutz-Jeghers syndrome, and Metenier's disease) every 1 to 2 years.[11] Mass endoscopic/radiologic screening is not recommended in low-incidence areas such as Canada and the United States.[11]

Diagnosis and Staging

Endoscopy is regarded as the most sensitive and specific diagnostic method in patients suspected of harboring gastric cancer.[12] Endoscopy allows direct visualization of tumor location, the extent of mucosal involvement, and biopsy (or cytologic brushings) for tissue diagnosis.[38] When combined with endoscopy and radiologic modalities, endoscopic ultrasound (EUS) can maximize tumor staging by providing information about depth of tumor invasion and assess the extent of perigastric lymphadenopathy. Willis et al[39] suggest that EUS is currently the most valuable diagnostic tool for preoperative staging of gastric cancer (82% accuracy in assessing the depth of tumor invasion) and for

determining tumor resectability. Karpeh et al[12] suggest the combined use of EUS and laparoscopic staging facilitates patient selection by providing information about tumor depth and perigastric lymph node involvement. They do caution, however, that EUS is less accurate (50–87%) in determining lymph node status.

An upper gastrointestinal barium study (UGI) involves the instillation of liquid barium into the stomach and a combination of 4 techniques: barium-filled evaluation, double-contrast, mucosal relief views, and compression views of the stomach.[40] The procedure permits identification of mucosal irregularities. Halvorsen et al[40] have suggested that, although endoscopy is increasingly becoming the method of choice, the 2 methods are complementary and have equivalent diagnostic efficacy.

Computed tomography (CT) is the most frequently used modality for staging gastric cancer.[40] CT can detect liver metastases, regional and distant lymphadenopathy, and can predict direct invasion of adjacent structures. Kuntz et al[41] suggested that CT has a sensitivity of 88% for tumor detection. The ability of CT to accurately determine either tumor infiltration (T stage 58%) or perigastric lymph node status (25–86%) varied widely and was not considered a reliable predictor of disease extent in several studies.[41–43]

Magnetic resonance imaging (MRI) has had limited use in the staging of gastric cancer primarily as a result of difficulties with motion artifact, cost, time required for examination, and lack of an appropriate oral contrast agent.[44,45] However, in a recent study comparing MRI with CT, Sohn et al[44] documented advanced gastric cancers were easily detected with both techniques. They showed MRI was slightly better than CT in the T staging of gastric cancer.[44] Similarly, Kim et al[46] documented T staging accuracy of MRI was superior to CT (81% vs. 73%, $P < 0.05$). This study suggested MRI was prone to overstaging pathologic tumor thickness.[46] Overall T staging accuracy has been reported to be between 73% and 88%.[45] The use of MRI in N staging has been hindered by the same difficulties encountered with CT staging, in which nodal status is judged on the basis of lymph node size. Several studies show the accuracy of MRI nodal staging is inferior to CT staging (65% vs. 73% respectively, $P > 0.05$), with both techniques tending to understage nodal status.[45,46] Finally, Motohara et al[45] reviewed the ability of MRI to detect extragastric metastases and concluded MRI had a greater sensitivity than CT in detecting liver, bone, and peritoneal dissemination. The obvious advantage of MRI staging lies predominantly with its multiplanar capabilities, lack of ionizing radiation, and use in patients with contrast hypersensitivity.[44] Other staging modalities include abdominal ultrasound, positron emission tomography scans, and staging laparoscopy.[36]

SURGICAL THERAPY

Total Versus Subtotal Versus Proximal Gastrectomy

Choice of surgical procedure in resectable gastric cancer is dictated by size, location, and ability to achieve surgical margins free of gross and microscopic disease. Several European studies have shown that to achieve adequate margins clear of disease, there must be a 5-cm distance from the tumor to the closest resection line in intestinal-type and 10-cm margins in diffuse-type tumors.[39,47–49]

In general, tumors confined to the proximal third of the stomach are treated with total gastrectomy to ensure adequate resection margins. It is controversial whether proximal gastrectomy is associated with poor functional outcome of the distal gastric remnant compared with a total gastrectomy with reconstruction. Although there are few studies to address this issue, Harrison et al,[50] in a retrospective review, demonstrated that patients with proximal gastric cancer who underwent total gastrectomy or proximal gastrectomy had similar overall survival times and recurrence rates. This study suggested both procedures could be accomplished safely. The authors suggest, although the 2 procedures are equivalent from a survival and recurrence perspective, further studies are necessary to assess nutrition and quality of life. Studies have demonstrated improved quality of life in the subtotal gastrectomy over the total gastrectomy group[51–53]; however, only 1 study[53] specifically demonstrated a reduced quality of life of proximal gastrectomy over total and distal subtotal resections.

There remains controversy surrounding the choice of procedure for tumors of the middle and distal thirds of the stomach. In a large European survey involving 62 centers, Heberer et al[54] demonstrated that 44% of surgeons prefer a total gastrectomy for diffuse-type gastric cancer of the antrum based on improved tumor clearance and local recurrence rates. In an analysis of 6400 patients in the U.S. National Cancer Database, Hundahl et al[13] showed that 12.3% of patients with cancer of the antrum or pylorus, regardless of tumor type, were treated with total gastrectomy. In a multicenter randomized trial of 618 patients, Bozzetti et al[1] concluded that patients with cancer of the middle and distal third of the stomach, who underwent either subtotal or total gastrectomy, had the same 5-year survival. This study showed patients undergoing subtotal gastrectomy had shorter hospital stays, better nutritional status, fewer complications, and better quality of life.[1] Furthermore, patients undergoing total gastrectomy had higher splenectomy rates with increased postoperative complications and susceptibility to infection, supporting the role of subtotal gastrectomy when possible.[1] The authors concluded that should a gastric cancer involve adjacent organs, these organs should be removed *en bloc* with the stomach, provided a combined procedure achieves clear resection margins.[47,48]

Limited Versus Extended Lymphadenectomy

The incidence of lymph node involvement ranges from 3% to 5% for tumors limited to the mucosa, 16% to 25% for those limited to the submucosa, and 80% to 90% in patients presenting with stage III or IV disease.[11,55] There is considerable controversy regarding the appropriate extent of lymph node dissection (LND). Retrospective studies from Japan, involving more than 10,000 patients, suggest extended LND combined with gastrectomy prolongs survival compared with limited LND.[56–59] The extended LND produced overall 5-year survival of 50% to 62% versus 15% to 30% obtained for limited resections in the United States.[10,58,60] Japanese investigators assert that the extended LND (D2) removes tumor in the regional lymph nodes before it can metastasize. In addition, it is argued that extended LND improves staging accuracy.[55–59]

The discrepancy in overall survival rates between Japanese and Western centers after extended LND led to 2 large multicenter randomized, prospective trials. The Dutch Gastric Cancer Group[61] randomized 711 patients (380 to limited [D1] and 331 to extended [D2]) to undergo resection with curative intent. This trial showed that patients in the D2 group had a significantly higher rate of postoperative complications than did those in the D1 group (43% vs. 25%; $P < 0.001$), more postoperative deaths (10% vs. 4%; $P = 0.004$, and longer hospital stays (median, 16 vs. 14 days; $P < 0.001$).[61] Furthermore, the 5-year survival rates were similar in the 2 groups (45% in the D1 group and 47% in the D2 group).[61] In the Dutch trial, the authors noted stage migration occurred in 30% of the D2 group and may have explained the East versus West difference in survival in patients matched for stage.[61] The authors concluded the results did not support the routine use of D2 LND. However, in a subgroup analysis, they showed a significant difference in patients with stages II and IIIA offered a D2 resection, an observation supported by Siewert et al[62] in the German Gastric Cancer Study. Furthermore, Hundahl et al,[13] examining the mature results of the Dutch Trial, noted a risk of recurrence greater in the D1 than in the D2 group (41% vs. 29%; $P = 0.02$), supporting the role of an extended lymph node resection.

Cuschieri et al[63] conducted a randomized comparison of D1 (n = 200) versus D2 (n = 200) resections for potentially curable advanced gastric cancer in the Medical Research Council (MRC) trial. The results of the trial demonstrated a significant difference between the D2 group and the D1 group in postoperative mortality (13% vs. 6.5%; $P = 0.04$) and morbidity (46% vs. 28%; $P < 0.001$), with no difference in overall 5-year survival for D2 versus D1 (33% vs. 35%).[63] Similar to the Dutch trial, the MRC demonstrated no survival advantage with the classic Japanese extended resection; however, a subgroup analysis of the MRC trial demonstrated several interesting results. First, the greatest contributing factor to postoperative morbidity and mortality in the D2 group was the addition of a pancreaticosplenectomy (hazard ratio, 1.53; CI, 1.17–2.01).[63] Second, preservation of the pancreas and spleen with an accompanying D2 resection may carry a better survival than a D1 resection and can be carried out with low postoperative morbidity and mortality.[63] Interestingly, in both the Dutch and MRC trials, when a minimum of a D1 resection (removal of at least the N1-level nodes) was mandated for all patients, the overall 5-year survival of the D1 group jumped from a 20% survival to 34% (MRC) and 45% (Dutch), again suggesting a strong association between survival and an adequate LN dissection.[13] Cuschieri et al[63] concluded that a "D2 resection without pancreatico-splenectomy may be better than a standard D1 resection, and cannot be dismissed by the results of this trial."

Several follow-up studies based on the Dutch and MRC results have examined the role of extended LND with pancreas and spleen preservation on postoperative morbidity, mortality, and overall survival.[10,55,56,62,64–69] These studies demonstrated extended LND with preservation of the spleen and pancreas can be performed with postoperative morbidity and mortality equivalent to limited LND. Several well-conducted prospective studies[10,62,64–66,69] demonstrated extended LND is not associated with an increase in morbidity or mortality when conducted in experienced centers and markedly improves long-term survival in patients with stage II, IIIA[10,62,64–66,69] and perhaps IIIB disease.[10] Based on these studies, gastrectomy with extended lymph node dissection remains the procedure of choice in specialized centers.[56,69–73]

New Issues With Lymphadenectomy for Gastric Cancer

Early editions of the TNM staging criteria were concerned with N status as defined by the location of lymph node (LN) metastasis relative to the primary tumor.[74] This created controversy with respect to appropriate lymph node resections, and prevented generalizability with Asian studies staged with the Japanese Classification for Gastric Carcinoma (JCGC).[75] The JCGC categorized the extent of LN metastasis on the basis of anatomic LN station (Table 1). The presence of metastasis in each LN group reflects the N status and forms the basis of the D categories (Table 1).[74] With the recognition of the survival advantage of extended (D2) resections, the fifth edition of the AJCC TNM has been modified to include available clinical, radiologic, endoscopic, and surgical means to assess the extent of disease.[76] The fifth edition classifies LN metastasis based on the number of positive nodes, in which at least 15 LN must be dissected and examined for staging to be accurate (Table 2).[75,76] In a historical cohort, Karpeh et al[75] demonstrated the number of positive nodes provided a better prognosis than anatomic location, as defined by an earlier TNM edition. Similarly, Kodera et al[77] applied the 1997 TNM staging to 493 Japanese patients who had a D2

TABLE 1. Japanese Classification for Gastric Carcinoma (JCGC)

Lymph Node Group	Anatomic Location	D Category
Group 1	Left cardiac, right cardiac, greater and lesser curvature supra- and infrapyloric	D1
Group 2	Left gastric, common hepatic, splenic artery, splenic hilum hepatic proper, celiac	D2
Group 3	Lepatoduodenal, posterior pancreas, root of mesentery, paraesophageal, diaphragmatic	D3

D indicates extent of surgical resection according to Western nomenclature; D1, group 1; D2, groups 1 + 2; D3, groups 1+ 2 + 3 + paraaortic dissection.

Reprinted from Karpeh MS, et al. *Ann Surg.* 2000;232:362–371.

or D3 resection and concluded the number of involved nodes was a strong prognostic indicator that should replace the N category in the JCGC. This finding has since been supported by several groups that similarly found increased LN number improves prognostication, minimizes the effects of stage migration, improves nodal staging across regions and countries, aids appropriate multimodality therapy selection, and provides a better indication of disease burden.[75,76,78] In 1995, pathologic N stage was defined by the number of metastatic LN, thereby achieving a single uniform staging system.[75]

Although not completely accepted, there is increasing consensus that retrieving at least 15 LN is necessary to accurately stage a tumor. However, there is considerable noncompliance by North American and European surgical centers. Mullaney et al[76] showed only 31% (range, 10–44%) of surgically resected cases could be accurately assessed for lymph node status. The paucity of LN for staging has implications for both prognosis and stage migration.[76] This observation was supported in a study that examined 1038 patients in a single American institution and found that up to 27% of cases had fewer than 15 nodes examined.[75] Even more alarming was the report from the U.S. National Data Base, which demonstrated that as few as 18% of U.S. patients have ≥15 LN analyzed.[13] The authors suggest there is a high likelihood of residual, untreated regional lymph node disease in these patients. Noncompliance may be a failure in acceptance of extensive resections to improve prognosis, lack of familiarity with the extent of resection necessary to achieve the minimum LN count, and inadequate pathologic assessment.[13,75,76,78]

Adjuvant or Neoadjuvant Therapy

Patients with localized node negative gastric cancer have 5-year survival rates that approach 75% when treated with surgery alone.[79] This is in contrast to patients with lymph node involvement, in whom survival rates range from 10% to 30%.[9] The outcome of gastric cancer is complicated by a high incidence of local recurrence and distant metastases after curative surgery and has prompted interest in adjuvant therapies in the hope of improving treatment outcome.[58] Studies of adjuvant and neoadjuvant therapy in the treatment of gastric cancer have produced conflicting results. The inconsistency may be a reflection of the differences between populations studied (high- vs. low-risk groups),[80] pathologic classification,[81] extent of surgical procedure (D2 vs. D1)[68] as well as differences in the content and timing of adjuvant therapy (immediate vs. delayed). Several metaanalyses[82–88] have been published in attempt to address discrepancies reported in the literature, the findings of which are summarized in Table 3.

Three of 7 metaanalyses suggest a small but significant advantage of adjuvant chemotherapy in the treatment of completely resected gastric cancer.[83,84,87] However, these authors suggest the results be interpreted with caution, because the results are of borderline significance[83] and may be influenced by a series of biases as well as poor methodologic quality.[84] This conclusion reflected an earlier report that reviewed the results of 43 randomized trials between 1967 and 1993 concerning all adjuvant therapies for gastric cancer, including those published in the Japanese literature.[89] This review concluded that the results from North American and European randomized trials did not support the routine use of adjuvant chemotherapy for gastric cancer.[89]

Janunger et al,[85] in a systematic overview of 153 scientific papers (involving 12,367 patients), examined the effects of adjuvant chemotherapy in gastric cancer. In their metaanalysis, a significant overall survival benefit was demonstrated (Table 3). However, separate analysis of Western and Asian studies demonstrated a significant difference in outcome in Asian (OR, 0.58; 95% CI, 0.44–0.76), but not in Western (OR, 0.96; 95% CI, 0.83–1.12) reports, a difference attributed to timing of diagnosis, extent of surgery, and stage migration.[85] In a more recent metaanalysis, Junnunger et al,[88] applying modern drug combinations over the last 10 years, failed to demonstrate any significant survival benefit (Table 3). Overall, there is insufficient evidence at present to recommend postoperative chemotherapy as standard adjuvant treatment in Western centers.[82–85,88]

Neoadjuvant therapy (chemotherapy, chemoradiotherapy, radiation, or immunotherapy, either alone or in combination) has been used with locally advanced tumors and those with a high risk of recurrence despite apparently curative surgery. Resectability rates of 40% to 100% and potentially curative resections in 37% to 80% of cases have been reported.[85] However, only 2 randomized trials have addressed neoadjuvant chemotherapy therapy, neither of which convincingly demonstrates clear benefit.[90–92] Studies regarding

TABLE 2. American Joint Committee on Cancer (AJCC) Classification of Gastric Cancer (5th Edition)

T = Primary Tumor			
Tx	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ		
T1	Invades lamina propria/submucosa		
T2	Invades muscularis propria/subserosa		
T3	Penetrates serosa		
T4	Invades adjacent structures		
N = Lymph Node Status			
Nx	Regional lymph nodes cannot be assessed		
N0	No regional lymph nodes involved		
N1	Metastasis in 1–6 regional lymph nodes		
N2	Metastasis in 7–15 regional lymph nodes		
N3	Metastasis in more than 15 regional lymph nodes		
M = Distant Metastasis			
Mx	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
Stage Grouping			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T1	N1	M0
	T2	N0	M0
Stage II	T1	N2	M0
	T2	N1	M0
	T3	N0	M0
Stage IIIA	T2	N2	M0
	T3	N1	M0
	T4	N0	M0
Stage IIIB	T3	N2	M0
Stage IV	T4	N1, N2, N3	M0
	T1, T2, T3	N3	M0
	Any T	Any N	M1

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adjuvant intraperitoneal chemotherapy are similarly inconclusive and are not administered routinely outside the clinical trial setting.[85]

Preliminary studies of adjuvant chemoradiotherapy showed promising results in patients resected with curative intent.[93,94] The role of adjuvant chemoradiotherapy was examined primarily in the Intergroup 0116 trial[95] that randomized 566 patients with stage IB-IVM0 completely resected gastric or gastroesophageal adenocarcinoma to receive surgery alone or surgery plus chemoradiotherapy (5f + leucovorin followed by 45 Gy of radiation). The surgery alone arm fared significantly worse when compared with the adjuvant chemoradiotherapy arm in terms of relapse-free survival (hazard ratio, 1.52; 95% CI, 1.23–1.86) and death (hazard ratio, 1.35; 95% CI, 1.09–1.66).[14] The addition of adjuvant chemoradiotherapy improved median survival significantly ($P = 0.005$) from 27 months to 36 months.[14] Distant relapse was the most common site of recurrence in the adjuvant group (33% vs. 18%), whereas local recurrence was more common in the surgery-only group (29% vs. 19%).[14] Significant toxicity (grade 3 or higher) was observed in the chemoradiotherapy group, with 3 patients (1%) dying of treatment-related toxicity. Furthermore, although the surgical protocol recommended an extensive lymph node resection, less than 10% of patients received a formal D2 dissection, whereas 54% underwent a D0 dissection.[14] The authors conclude the greatest benefit of chemoradiotherapy may be in high-risk patients treated with inadequate D2 resections.

TABLE 3. Meta-analyses of Randomized Clinical Trials of Adjuvant Chemotherapy

Reference	Patients	RCT	OR	95% CI	*P* Value
Hermans et al.[85]	2096	11	0.88	0.78–1.08	NS
Earle et al.[86]	1990	13	0.80	0.66–0.97	0.024
Mari et al.[87]	3658	20	0.82	0.75–0.89	<0.001
Janunger et al.[88]	3962	21	0.84	0.74–0.96	N/A
Panzini et al.[89]	3118	17	0.72	0.62–0.84	N/A
Hu et al.[90]	4543	14	0.56	0.40–0.79	<0.001
Janunger et al.[91]	1928	25	0.94	0.77–1.14	NS

Significance is noted by *P* value <0.05; NS, not significant; N/A, not reported.

Patients, indicates number of patients included in metaanalyses; RCT, randomized clinical trial and number of studies included in the metaanalyses; 95% CI, 95% confidence interval.

Despite the results of this study, some institutions recommend adjuvant chemotherapy alone in patients unable to tolerate radiotherapy; however, the optimal regimen in this setting has yet to be defined.[92]

Unresectable Locally Advanced or Metastatic Disease

Greater than 50% of patients present with unresectable locally advanced or metastatic gastric adenocarcinoma.[96] The majority of patients, including those with early-stage disease, develop metastases at some point during the course of their illness. Symptom palliation in this group of patients is paramount and can be thought of in terms of either local and/or systemic therapy. Treatment of local symptoms includes palliative surgery, radiation, and/or endoscopic procedures. In patients with metastatic disease, systemic chemotherapy is the only treatment modality that has demonstrated a significant improvement in survival.[88] In selected patients with good performance status, compared with best supportive care alone, combination chemotherapy has been shown to improve median survival by 3 to 9 months, as well as demonstrating improvement or maintenance of quality of life.[97–100] Numerous traditional single-agent chemotherapy regimes have been studied, with a variety of combinations evaluated in phase III trials demonstrating response rates of 25% to 40%.[101] Despite the number of regimens evaluated, no single combination regimen has emerged.[88] Standard protocols in North America include epirubicin, cisplatin and continuous infusion 5FU (ECF),[102] cisplatin and 5-day infusion 5FU (CF), and etoposide, leucovorin, and bolus 5FU (ELF).[103] Third-generation combination regimens have incorporated newer agents such as irinotecan, oxaliplatin, and taxanes, all of which are currently under phase II–III evaluation. Despite the use of traditional combination chemotherapy, median survivals rarely surpass 10 months.

PROGNOSTIC VARIABLES

Stage

The pathologic stage has consistently been shown to be of prognostic significance for both 5-year survival and local recurrence rates.[62,104–106] Siewert et al,[62] in a prospective multicenter observation study, demonstrated a lymph node ratio greater than 20% (between positive and removed nodes) was the single most important independent prognostic factor ($P < 0.0001$), followed by residual tumor status ($P < 0.0001$) and T category ($P < 0.0001$). In a multivariate subgroup analysis of completely resected tumors (R0), they confirmed nodal status was the most important predictor, followed by T category.[62]

Grade

Grade refers to the degree of differentiation of tumor cells and has been shown to correlate with the aggressiveness of the neoplasm.[6] Pathologic grade classifies tumors into 1 of 3 categories: well, moderately, or poorly differentiated/anaplastic.[6] Although grade is routinely reported in pathologic reports, the prognostic impact in gastric cancer remains to be elucidated, because several retrospective studies have failed to identify grade as an independent prognostic factor.[106–108]

Size

Size of the primary tumor, measured in greatest dimension, has been identified in several retrospective studies to be of prognostic significance.[9,105,106] These studies suggest increasing tumor diameter is associated with lymph node metastasis and 5-year survival. This was confirmed in a prospective, randomized trial that demonstrated tumor size to be an independent prognostic factor in a multivariate analysis ($P = 0.0002$; CI, 1.3–2.2) in patients with tumor-free margins.[62]

Tumor Location

The influence of tumor location has several important implications in the treatment and prognosis of gastric cancer.

Although there are studies that have shown no association between location and prognosis,[105,107–109] several studies have shown that gastric carcinoma of the proximal third of the stomach represents a distinct clinical entity with prognostic implications.[2,9,11,105,106,110,111] A recent study suggested proximal tumors have a higher frequency of larger size, extensive wall penetration, venous invasion, nodal metastasis, and more advanced stage, with an overall worse survival relative to distal tumors.[111] Proximal tumors may require a different surgical approach based on a potentially different biologic behavior.

Lymphatic and Vascular Invasion

The presence of tumor emboli within peritumor vessels and lymphatics has recently generated interest as a potential independent prognostic indicator. Studies have demonstrated that lymph node involvement is a statistically significant predictor of survival, and the presence of tumor emboli significantly influences tumor recurrence and death after curative resection.[72,105,110] Yokota et al[110] found lymphatic invasion retained its significance (relative risk, 11.43; CI, 2.63–49.55), even in competition with other significant variables in multivariate analysis. These findings were recently supported in a report by Hyung et al,[112] who reported a poor prognosis associated with advanced T stage and the presence of vascular invasion. Kooby et al[113] similarly demonstrated, in adequately staged node-negative patients, vascular invasion was an independent negative prognostic factor and may be a predictor of biologic aggressiveness.

Age and Gender

Neither age nor gender have been shown definitively to be of prognostic significance for death from recurrent or metastatic cancer.[62,109,114] Two small retrospective studies in a subgroup analysis identified age as a significant prognostic variable,[105,108] whereas in another study, the influence of age was not of independent prognostic value.[114] This study determined that survival was determined by stage and completeness of resection.

Other Factors

Several other factors have been implicated with increased local recurrence and decreased survival in gastric cancer. Putative tumor markers (p53, E-cadherin, CD-34, c-ErbB2, CA 72–4, CEA) have recently gained popularity as potential prognostic indicators for predicting tumor behavior.[111,115–117] These markers are likely to gain importance as the field of gene-expression analysis continues to expand.[117] Other factors include tumor perforation, emergency surgery, and blood transfusion.

Survival Analysis and Its Application to Gastric Cancer

The use of determining the prognosis of a disease is 2-fold. Prognostication provides information to patients and clinicians of the future course and natural history of the disease and allows for comparative analysis of a given outcome between 2 or more populations.[118,119]

Prognostic studies often involve comparisons between 2 or more groups of patients that differ with respect to their disease status. Survival curves for each group may be constructed and the respective curves compared by the log rank test.[118] Alternatively, multivariate models may be used to incorporate both time and the effects of multiple factors on the time to a given outcome into the analysis.[118] This analysis may be used to identify a combination of factors that best predict the prognosis in a group of patients or the effect of individual factors independently.

The methods of survival analysis have been widely applied to the study of gastric cancer to determine the significance of prognostic factors in guiding clinical decision-making. Recently, survival studies have generated multivariate predictive models based on clinicopathologic factors and linked them to molecular pathways. This approach incorporates gene expression profiles, representing the biologic behavior of tumors, generated from microarray studies into predictive models, and may be used to guide surgical and adjuvant therapy.

Future Directions

Some epithelial cancers appear to follow the multistep pathway of carcinogenesis. In these tumors, the correlation between genetic abnormalities and sequential phenotypic changes has allowed accurate clinical and pathologic characterization.[36,120–123] However, gastric cancer exhibits heterogeneity in histopathology and molecular changes that has impeded its complete molecular delineation.[121] Only a few genes (eg, c-met, c-erbB2, K-sam, E-cadherin) are implicated in gastric cancer.[124] Of these, only E-cadherin has been linked definitively as a marker of hereditary diffuse gastric cancer.[23,25–27,35] As mentioned, most gastric cancers occur sporadically, with 8% to 10% having an inherited familial component. More commonly, gastric cancers occur without any consistent mutation abnormality. There is considerable variation in the pathogenesis ranging from a stepwise progression of changes (gastritis → metaplasia → invasive carcinoma) to tumors arising in the absence of a precursor lesion.[121] Novel technologies such as microarray-based gene expression profiling are providing information on the expression of many genes involved in human cancers.[125] This approach is promising to transform our understanding of the molecular interactions that ultimately describe a tumor phenotype and behavior.

Microarray-Based Gene Expression Profiling

DNA sequences do not tell us how gene expression gives rise to phenotype or how gene expression alters downstream molecular byproducts.[126] Current limitations to under-

standing gastric carcinogenesis are techniques to link structural knowledge of genes to functional changes that occur between component parts, thereby providing insight into tumor behavior.[124,126,127] Characterization of genes that are differentially expressed in gastric cancer is essential for accurate diagnosis and tumor characterization and for informed surgical and adjuvant therapy decision-making, development of novel therapeutics, and delineation of tumor behavior for more accurate prognostication.[124]

Microarrays have extended molecular research beyond the candidate gene approach and are beginning to establish a link between gene expression and functional interactions.[121,124–129] An advantage of microarrays is that it is a translational tool that incorporates functional interactions in an attempt to understand biology, not simply to identify the component parts of a pathway.[126] Gene expression studies allow characterization of genes that are differentially expressed or transcribed from the genomic DNA.[122,124] The resulting collection of genes, referred to as the expression profile, is considered to be a major determinant of cellular phenotype and function.[126] Understanding the differences in gene expression between normal tissue and malignant tissue, as well as the gene expression response to environmental stimuli, is central to understanding regulatory mechanisms involved in cancer development and progression.[125,126,129]

Multivariate regression analyses have been applied extensively in the study of cancer. These studies have allowed the determination of a large number of important clinicopathologic factors to guide clinicians with respect to management strategy. Despite this, traditional prognostic factors have limited predictive power and have changed current management strategies in only a few cancer types.[130] However, microarray technology coupled with multivariate predictive models has generated interest in the use of gene expression profiles as prognostic models.

Lymph node status, receptor status, proto-oncogenes, and gene mutations have all been correlated to prognosis in breast cancer.[131] However, breast cancer is complex, and knowledge about individual prognostic factors provides limited information about the biology of breast cancer. Several recent studies linking novel gene expression data to multivariate prognostic models have been used to examine survival and to develop more precise markers of biologic behavior to overcome the limitations of current predictive modeling techniques.[130–132] These studies have demonstrated that microarray analysis can accurately identify distinct subclasses of breast cancer[131,132] and independently predict overall and relapse-free survival based on "predictive gene sets" that are superior to currently available clinical and histologic prognostic models.[130,132]

The application of microarray analysis to diseases such as nonsmall cell lung cancer, hepatocellular carcinoma, esophageal carcinoma, and Barrett's esophagus have similarly shown the use of microarray in documenting distinct prognostic groups, molecular staging systems, models capable of accurately predicting overall, and disease-specific survival and recurrence rates beyond current techniques.[133–135] The application of gene expression profiles may therefore have the potential to refine diagnosis, prognosis, and patient management.[134]

The majority of microarray studies examining gastric adenocarcinoma have been aimed at developing exploratory gene profiles of gastric tumor or gastric cancer cell lines to identify gastric cancer-related genes, delineate molecular phenotypes, demonstrate tumor subtypes, and identify functional gene clusters as potential markers of biologic behavior.[124,136–141] There are few studies that have applied combined microarray and predictive modeling methodology to gastric cancer. Recent studies have shown that microarray, in combination with statistical modeling, accurately predicted tumor behavior with respect to tumor progression, metastatic potential, tumor recurrence, and overall prognosis.[142,143] Although in its infancy, gene expression analysis, combined with predictive models, holds promise in extending our understanding of gastric carcinoma. The relative paucity of data available relating gastric cancer gene profiles with prognosis and the success across various other cancers strongly reinforces the need for further exploration of this technique. With techniques capable of amplifying small quantities of tumor RNA, it is conceivable that endoscopically obtained tissue samples may be used to generate preoperative predictive gene clusters. In doing so, the identification of functional gene clusters may allow improved selection of patients for neoadjuvant and adjuvant therapy, tailored surgical resections, identification of novel gene clusters for targeted therapy design, and improved prognostication to facilitate both clinician and patient decision-making.

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